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**Cell penetrating peptide functionalized perfluorocarbon nanoemulsions for targeted cell labeling and enhanced fluorine-19 MRI detection.**

**Journal:** Magn Reson Med

**Publication Year:** 2020

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**PubMed link:** 31631402

**Funding Grants:** Molecular Imaging for Stem Cell Science and Clinical Application

**Public Summary:**

A bottleneck in developing cell therapies for cancer is assaying cell biodistribution, persistence and survival in vivo. Ex vivo cell labeling using perfluorocarbon (PFC) nanoemulsions, paired with <sup>19</sup>F MRI detection, is a non-invasive approach for cell product detection in vivo. Lymphocytes are small and weakly phagocytic limiting PFC labeling levels and MRI sensitivity. To boost labeling, we designed PFC nanoemulsion imaging probes displaying a cell-penetrating peptide, namely the transactivating transcription sequence (TAT) of the human immunodeficiency virus. We report optimized synthesis schemes for preparing TAT co-surfactant to complement the common surfactants used in PFC nanoemulsion preparations.

**Scientific Abstract:**

**PURPOSE:** A bottleneck in developing cell therapies for cancer is assaying cell biodistribution, persistence, and survival in vivo. Ex vivo cell labeling using perfluorocarbon (PFC) nanoemulsions, paired with (<sup>19</sup>) F MRI detection, is a non-invasive approach for cell product detection in vivo. Lymphocytes are small and weakly phagocytic limiting PFC labeling levels and MRI sensitivity. To boost labeling, we designed PFC nanoemulsion imaging probes displaying a cell-penetrating peptide, namely the transactivating transcription sequence (TAT) of the human immunodeficiency virus. We report optimized synthesis schemes for preparing TAT co-surfactant to complement the common surfactants used in PFC nanoemulsion preparations. **METHODS:** We performed ex vivo labeling of primary human chimeric antigen receptor (CAR) T cells with nanoemulsion. Intracellular labeling was validated using electron microscopy and confocal imaging. To detect signal enhancement in vivo, labeled CAR T cells were intra-tumorally injected into mice bearing flank glioma tumors. **RESULTS:** By incorporating TAT into the nanoemulsion, a labeling efficiency of ~10(12) fluorine atoms per CAR T cell was achieved that is a >8-fold increase compared to nanoemulsion without TAT while retaining high cell viability (~84%). Flow cytometry phenotypic assays show that CAR T cells are unaltered after labeling with TAT nanoemulsion, and in vitro tumor cell killing assays display intact cytotoxic function. The (<sup>19</sup>) F MRI signal detected from TAT-labeled CAR T cells was 8 times higher than cells labeled with PFC without TAT. **CONCLUSION:** The peptide-PFC nanoemulsion synthesis scheme presented can significantly enhance cell labeling and imaging sensitivity and is generalizable for other targeted imaging probes.

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